REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at (858) 720-5133.

Status of the Claims

Pending claims

Claims 31, 34, 35, 114, 115, 132 to 154 and 189 to 215 are pending. These claims have been examined to the extent they are drawn to the elected species SEQ ID NO:2 and self-assembly as a way of polymerizing.

Claims added in the instant amendment

Claims 216 to 223 are added; claims 205 to 206, are canceled, without prejudice or disclaimer. Thus, after entry of the instant response, claims 31, 34, 35, 114, 115, 132 to 154 and 189 to 204 and 207 to 223 will be pending.

Outstanding Rejections

Claims 34, 114, 115, 134, 140 to 154, 189 to 200, 202 to 206, 214 and 215 are rejected under 35 U.S.C. § 112, second paragraph. Claims 31, 34, 114, 115, 134, 140 to 154, 189 to 206, 214 and 215, are rejected under 35 U.S.C. § 112, first paragraph, written description requirement – as a new matter rejection. Claims 31, 34, 114, 115, 134, 140 to 154 and 189 to 201, are rejected, under 35 U.S.C. § 112, first paragraph, enablement requirement.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Accordingly, Applicants respectfully submit that no new matter is introduced by the instant amendment.

Group Restriction Requirement and Election

The Office alleged that the pending claims of the application are directed to six (VI) separate and distinct inventions under 35 U.S.C. §121. In response to the Group Restriction Requirement, Applicants elected Group I, drawn to, inter alia, methods of producing polymers of conjugates of monomeric and non-monomeric polypeptides.

Issues under 35 U.S.C. §112, second paragraph

Claims 34, 114, 115, 134, 140 to 154, 189 to 200, 202 to 206, 214 and 215 are rejected under 35 U.S.C. § 112, second paragraph, for reasons set forth in detail on page 3, of the OA. The instant amendment addresses these issues.

Issues under 35 U.S.C. §112, first paragraph, written description requirement

New Matter

Claims 31, 34, 114, 115, 134, 140 to 154, 189 to 206, 214 and 215, are rejected under 35 U.S.C. § 112, first paragraph, written description requirement – as a new matter rejection, for reasons set forth on page 4, of the OA. The instant amendment addresses this issue. The term "non-monomeric" is deleted.

Enablement

Claims 31, 34, 114, 115, 134, 140 to 154 and 189 to 201, are rejected, under 35 U.S.C. § 112, first paragraph, enablement requirement, for reasons set forth in on pages 4 to 7, of the OA.

The Office noted that the specification is enabling for self-assembly of the peptide SEQ ID NO:2 itself, or its conjugate with green fluorescent protein (see the last paragraph of page 4, of the OA).

However, it is alleged that the specification is not enabling for (i) self-assembly of the peptide SEQ ID NO:2 modified by an attachment (other than green fluorescent protein); or, (i) self-assembly of sequence-modified versions of peptide SEQ ID NO:2, wherein the sequence modification is a conservative amino acid residue substitution. These concerns regarding enablement are essentially the same as those expressed in earlier office actions, e.g., see the Final office actions of June 23, 2005, and September 09, 2004; and Applicant reiterate and expressly incorporate by reference their earlier responses, including those of June 19, 2006, and April 06,

2005, including the Rule 132 expert declarations submitted with those responses.

Based on their earlier responses and Rule 132 expert declarations, and the response and amendment set forth in this response, Applicants respectfully maintain the specification enables both self-assembly of the peptide SEQ ID NO:2 modified by any attachment, and self-assembly of sequence-modified versions of peptide SEQ ID NO:2, wherein the sequence modification is a conservative amino acid residue substitution, such that the skilled artisan could practice the claimed methods without undue experimentation.

The cited art supports modified protein self-assembly

While Applicants aver that the specification does provide reasonable enablement to the skilled artisan, they first respectfully submit that the Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention The Office has repeated its use of Urry, et al. (1992) Materials Res. Society Symposium Proceeding 255:411-422 ("Urry"); and, the abstract Jenekhe, et al. (2000) ACS, 220th, PMSE-268 (Abst. 268) ("Jenekhe") to support its *prima facie* case of lack of enablement.

However, neither Urry nor Jenekhe establish a reasonable basis to question the enablement provided for the claimed invention, for reasons set forth in Applicants responses of April 06, 2005, and August 27, 2004, both expressly incorporated herein. For the Office's convenience, the April 06, 2005, response is (in part) repeated (with emphasis added):

> The Urry article, entitled "Hierarchial and Modulable Hydrophobic Folding and Self-Assembly in Elastic Protein-Based Polymers: Implications for Signal Transduction," discusses folding and self-assembly properties of hydrophobic (apolar) and polar moieties of elastomeric polypeptides, in particular, elastic protein-based polymers, such as elastin. The effects of changes in amino acid sequence, ionization conditions (e.g., pH) and temperature on the hierarchical hydrophobic folding of a series of elastomeric polypentapeptides was studied. Urry concluded that hierarchical hydrophobic folding can be modulated by changing the degree of ionization or by changes in a number of intensive variables. Urry noted that changes in these variables can be used to drive folding/unfolding-assembly/disassembly transitions under isothermal conditions, and that these folding/unfolding-assembly/disassembly transitions can be used to achieve signal transduction (i.e., the translocation or transduction of free energy). Urry also concluded that the process of folding and the formation of tertiary and quaternary structures could be readily and predictably controlled by manipulating temperature and the degree of hydrophobicity in the polypentapeptide, see, e.g., the first paragraph, page 413, of Urry. It appears Urry was able to easily and simply identify changes in

protein sequence and folding conditions to drive a protein polymer assembly or disassembly reaction. In fact, Urry's data and conclusions actually support the idea that folding/unfolding-assembly/disassembly of a protein can be easily manipulated by readily identified and manipulated variables. Thus, Urry is not a reference that can establish a reasonable basis to question the enablement provided for the claimed invention.

The Jenekhe abstract, entitled "Self-assembly of Functional Mesostructures and Discrete Objects from Synthetic Polymers," summarizes their work regarding the formation of functional mesostructures. They noted that they synthesized amphiphilic rod-coil block co-polymers of diverse macromolecular architecture. Jenekhe noted that they found these polymers to self-organize into ordered supramolecular assemblies, e.g., vesicles, microtubules, smectic layers and periodic microporous nanostructured thin films. They noted that novel cooperative properties and tunable optoelectronic and photonic properties were observed in their self-organized, supramolecular assemblies. Jenekhe concluded that their results demonstrated the potential of self-assembling polymers for engineering complex, functional and three-dimensional periodic mesostructures of discrete objects. Jenekhe did not note any problems or technological difficulties in making their self-organized, supramolecular assemblies. Jenekhe's data and conclusions actually support the idea that self-assembling polymers can be used for engineering complex, functional and three-dimensional periodic mesostructures into discrete objects. Thus, Jenekhe is not a reference that can establish a reasonable basis to question the enablement provided for the claimed invention.

Applicants respectfully maintain that the Office has not met its initial burden to establish a reasonable basis to question the enablement provided for in the specification for the claimed invention. Accordingly, the Patent Office has not set forth a *prima facie* case of lack of enablement and the rejection under section 112, first paragraph should be withdrawn.

The claimed methods can be practiced without undue experimentation

Applicants respectfully maintain the specification enables both self-assembly of the peptide SEQ ID NO:2 modified by any attachment, and self-assembly of sequence-modified versions of peptide SEQ ID NO:2, wherein the sequence modification is a conservative amino acid residue substitution, such that the skilled artisan could practice the claimed methods without undue experimentation. As discussed by the cited references Urry and Jenekhe, conditions for initiating polymerization and maintaining a polymerized state may differ for different monomer reagents.

However, as declared by Dr. Nelson Barton in his Rule 132 declaration of April 06, 2005, determining and adjusting for optimal conditions for polymerization for any particular conjugated

(modified) monomer used to practice the methods of this invention was routine at the time of this invention; and determining what conservative amino acid residue substitutions are permissive for polymerization also was routine at the time of this invention – please see paragraph 7, page 2, of that declaration. In brief, Dr. Barton declared that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art for producing polypeptide polymers was very high. Dr. Barton declared that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art for determining conditions for self-assembly of protein conjugates of the invention was also very high. Dr. Barton declared that it would have been routine for the skilled artisan at the time of the invention to screen for and select conditions that facilitated self-polymerization of the claimed conjugates of the invention, whether these compositions comprised monomeric polypeptides having a modification comprising attachment of an enzyme, attachment of a nucleotide or a nucleotide derivative, or attachment of an lipid or lipid derivative, or attachment of a targeting molecule, or attachment of a vector.

Thus, although one of skill in the art at the time of this invention might have had to screen large numbers of compositions, whether large numbers of compositions (e.g., protein conjugates or conservative residue modification variants) needed to be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987), which was discussed in Applicants' response of July 17, 2003.

The proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See MPEP §2164.08, pg 2100-197, 8th ed., rev. 2, May 2004. `The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). MPEP §2164.06, pg 2100-192, 8th ed., rev. 2, May 2004.

The facts in In re Wands are sufficiently analogous to the instant application to help illustrate this point, as explained in the MPEP (§2164.06(b), pg 2100-195, 8th ed., rev. 2, May 2004):

> (B) In In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court reversed the rejection for lack of enablement under 35 U.S.C. 112, first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, the applicant carried out the entire procedure for making a monoclonal antibody against HBsAg three times and each time was successful in producing at least one antibody which fell within the scope of the claims.

In In re Wands, after considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407. In In re Wands, it was not necessary to provide a method to routinely identify *every* monoclonal antibody hybridoma made in any particular production round, or *every possible* monoclonal antibody that could bind the exemplary antigen. Nor was it necessary to produce a working specie after very antibody-making procedure. In fact, in In re Wands, the screening protocol was found sufficiently enabling even though only one antibody was identified after running three procedures.

Analogous to In re Wands, it is not necessary that the specification or the state of the art at the time of the invention describe a protocol where every, or even most, attempts at making a polymer comprising a monomer with a conservative amino acid residue variant within the scope of the invention, or a polymer comprising a modified monomer within the scope of the invention, are successful. Because proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims, as in In re Wands, the claimed methods are sufficiently enabled if a reasonable number of conjugated or sequence variant monomers used in these methods

are successfully made by protocols known in the art or described in the specification. As discussed above, using the teaching of the specification and other protocols known in the art at the time of the invention one skilled in the art could have successfully practiced the invention without undue experimentation. In other words, as declared by Dr. Barton, because it was routine for the skilled artisan at the time of the invention to screen for and select conditions that facilitated self-polymerization of conjugates used in methods of the invention, and because such screening protocols were sufficiently sophisticated and well known at the time of the invention, one of skill in the art could have practiced the claimed methods without "undue experimentation", according to the appropriate legal definition of this term, e.g., as in In re Wands.

Furthermore, also analogous to In re Wands, the instant specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples; see, inter alia, Examples 19 to 21, of the specification, and Dr. Barton's discussion, paragraphs 4 to 6, in his Rule 132 declaration of April 6, 2005. Because the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, and all of the methods needed to practice the invention were well known, and there was a high level of skill in the art at the time the application was filed, the instant specification did provide reasonable enablement commensurate with the scope of the claimed invention. Accordingly, the rejection under section 112, first paragraph, can be properly withdrawn.

Conjugating monomers before and after polymerization

Applicants thank the Office for noting there may be some ambiguity in claim 31 as to whether in the claimed method the monomer is conjugated before or after polymerization (see page 6, "response to arguments" section, of the OA). The instant amendment clarifies this issue; claim 31 is now directed to methods wherein the monomer is conjugated before polymerization, and new claims are drawn to methods where the monomer is conjugated after polymerization, i.e., the monomers are conjugated after the polymerization step.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the objections to the claims, and the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 564462010900. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Dated: _July 5, 2007_____

Respectfully submitted,

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